THE COMPLEXITY OF "MIXED" DEPRESSION:

A Common Clinical Presentation

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INTRODUCTION

Most clinicians use the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for diagnosis and classification and are aware of its advantages in terms of communication and treatment planning. On the other hand, diagnostic classification systems, such as the *DSM-IV,* cannot always grasp the full clinical nuance of a patient's condition and the potential implications for treatment. Presenting symptoms may not always fit conveniently within a single diagnostic category and the "left out" symptoms may have clinical relevance. For instance, some patients who meet full *DSM-IV* criteria for major depressive disorder (MDD) may also present with subthreshold manic symptoms, such as increased energy or the reduced need for sleep at the same time. In current research terms, and for the future *DSM-V* criteria, these patients with subthreshold bipolarity are classified as MDD with "mixed" features.[1–5]

In fact, the clinical presentation of "mixed" depression is not rare at all. In the National Institute of Mental Health (NIMH) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) program, the majority of bipolar depressed patients also presented with some concomitant manic symptoms.[6] In fact, less than one-third of these bipolar-depressed patients presented with no manic symptoms at all. However, they did not present with enough manic symptoms to meet *DSM-IV* criteria for mania. Although "mixed" depressed patients like these do not meet criteria for mania, they do have more complex psychopathology and more difficult treatment requirements.[1,3,6,7,8]

In this installment of Research to Practice, I interview Dr. Andrew A. Nierenberg, who is Professor of Psychiatry at the Harvard Medical School and Director of the Bipolar Clinic and Research Program at the Massachusetts General Hospital. In this interview, Dr. Nierenberg discusses the diagnostic issue of "mixed" depression, reviews the specific manic-type symptoms, and considers the implicit treatment dilemma.

What is "mixed" depression?

Dr. Nierenberg: "Mixed" depression is a clinical presentation in which a patient meets the full criteria for MDD and, at the same time, has a mixture of other features that are consistent with hypomania or mania. However, when only two or three of these manic symptoms are present, the duration fails to meet current criteria for hypomania (4 days) or mania (7 days), and therefore the diagnosis does reach

the full criteria for a hypomanic or manic episode.[2]

As the *DSM-IV* is currently constructed, for someone to meet the criteria for a "mixed" episode of bipolar disorder, they have to meet both full criteria for a major depressive episode and a manic episode at the same time. Anything short of meeting the full criteria for a manic episode does not count in the current way that the diagnostic system works. However, in reality, it turns out that many patients with bipolar disorder can have some manic-type symptoms when they get depressed. In the new way of thinking, these patients can have a "mixed" episode of depression with only some of these manic-type features.

The treating challenge is that some of the so-called manic-type symptoms may actually represent other clinical conditions. For instance, the agitation sometimes associated with mania can also be consistent with an agitated, nonmanic depressive episode or simply be a manifestation of the anxiety that goes along with depression in many patients. This creates a diagnostic dilemma for practicing clinicians.

What is the incidence of manic-type symptoms, including agitation, occurring in the general population of patients treated with antidepressants?

Dr. Nierenberg: It is hard to estimate how often that really happens. One source of data is the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study. STAR-D was a very large multicenter study that was done in a real-world setting, including academic and primary care settings, with more than 4,200 patients treated. The absolute incidence of antidepressant-induced mania, hypomania, and agitation was certainly less than one percent overall. The randomized study of antidepressants compared to placebo added to a mood stabilizer resulted in about 10-percent switching without any differences between the two groups. This finding is in sharp contrast to what is stated in the literature, where up to 30 percent of patients may present with either a history of subtle hypomanic symptoms in the past or they might get agitated. I believe the true incidence is somewhere between one percent and 30 percent.

This wide range highlights the importance of a very careful diagnostic assessment to see what the previous history of symptoms and treatment responses has been. Do you agree?

Dr. Nierenberg: Yes. Performing a systematic assessment helps. The ability to recall some of the subtleties of illness that have occurred in the past is difficult for anyone. Beyond that, when someone is depressed, he or she tends to remember the depressive symptoms in the past and to not remember the hypomanic symptoms. It is an affective-laden memory, which means that the current depressed state allows the patient to remember the same depressed symptoms from past episodes and to forget what happened when he or she was not in that state. The depression is painful to the patient, whereas the manic or hypomanic symptoms may not necessarily cause the patient particular distress. Or if the manic or hypomanic symptoms do cause the patient stress, he or she is not quite aware of them because the bright sun of the major depressive episode is overshadowing the pale moon of the hypomanic type of symptoms.

What are the actual manic-type symptoms that would comprise this "mixed features" kind of major depression?

Dr. Nierenberg: The classic symptoms include elevated mood, increased rate of speech, increased energy, decreased inhibition, racing thoughts, and a decreased perceived need for sleep. These are unequivocally classic symptoms of mania or hypomania in contrast to a nonspecific symptom, such as agitation.

How can you have elevated mood in a depressed patient?

Dr. Nierenberg: It might seem paradoxical. You might ask, "How can somebody meet the criteria for a major depressive episode if they also have an elevated or expansive mood?" The *DSM-IV* criteria for MDD indicate that an individual can have a severe decrease in interest without necessarily having a depressed mood. A depressed patient can have either the decreased mood or the decreased interest, or both, and still meet criteria for MDD.

The depressed mood may also be present only part of the time, and perhaps there is some cyclicity in which there may be times when the patient has expansive mood as well.

Moods vary in the course of a week, and it is very hard to capture hour-to-hour changes. And, in fact, many times the clinician will not want to know the hour-to-hour changes a patient experiences; the clinician will want an overall summary. But, if someone is feeling horrible in the morning and then feeling absolutely wonderful in the afternoon, it is hard to answer your question. So that is how you can have this "mixture" of what would appear to be polar opposites.

What about inflated self esteem in depressed patients?

Dr. Nierenberg: Depressed patients can also have an inflated self esteem or grandiosity. Sometimes the clinician needs to ask another person who knows the patient because the patient's ability to self observe and self

report can be quite limited in a depressed state. Of course, the clinician will need to differentiate between narcissistic personality disorder and grandiosity: It is one thing for a patient to think he or she is without fault, but it is another thing for the patient to have hypomanic symptoms such that he or she is not in his or her normal state of mind.

What about increased speech and racing thoughts?

Dr. Nierenberg: Regarding increased speech, understanding if it is a change from usual in the patient is critical There are some people who speak rapidly all the time, and there are some people who like to hear their own words (termed *logorrhea*)—they talk a lot. The clinician, therefore, must determine if the fast speech of a patient is different from their normal speech. Is the patient saying a lot of things in a rapid fire way and other people are not able to get a word in edgewise?

The other symptom is flight of ideas or racing thoughts. With the flight of ideas, a clinician should be able to determine if a patient is suffering from this symptom by observing that there are weak links between one thought verbalized by the patient and the next. There is a certain speed to the patient's verbalizations, but it would not be considered psychotic. In other words, with flight of ideas, there is not a completely dissociated sense with no train of thought at all, but rather, it seems one thought reminds the patient of something else, and then that reminds the patient of something else, and on and on, and the patient never really gets to the point. The patient will do this quite rapidly. It might sound like this: "I have a blue car, and the blue car is like the sky, and I remember flying in the sky and going off to Europe to go skiing, the skis are made of wood, and the wood comes from the yew tree, and the yew tree is associated with taxol..." The patient never makes a point. That is a flight of ideas.

Sometimes, true racing thoughts can be difficult to assess. If the clinician simply asks a patient if he or she has racing thoughts, many patients will say yes even if they do not exhibit them. If the clinician asks for an example, a patient might tell the clinician about the worries that are racing in his or her head. A patient may say to the clinician, "I'm worried about how I'm going to pay for these things..." or "My job is a mess..." or "I don't know what's going to happen to my house and my mortgage, and I can't stop worrying about these things." These thoughts are not racing thoughts. Racing thoughts are a subjective sense that thoughts are going more rapidly than they usually do and that it is hard to keep up with the internal dialogue because of the speed of the thoughts

What other manic-type symptoms occur in "mixed" depression?

Dr. Nierenberg: Another symptom is a sense of increased energy. In some ways, we mean this metaphorically. Does the patient actually think more clearly or is it just the absence of fatigue?

Most patients can tell a clinician when they feel energetic or when they feel that they have not only the motivation and the will, but that overall they can do a lot more than usual, or when they feel more alert than usual, perhaps even able to do more things motorically. But each patient will have some subjective sense of what "more energy" is. It is very important to ask the patient in what way his or her energy has increased.

Is increased energy associated with productivity as opposed to agitation?

Dr. Nierenberg: Increased energy does not mean that the patient is productive, although he or she may feel he or she is. In fact, one problem is that the patient may be able to do a lot of things but not finish anything. The patient may be doing a little of this and a little of that, mixed with distractibility, but the patient actually is not able to accomplish or complete anything.

Agitation can seem like increased energy to some people. There could be a restless type of energy that would be a form of physical agitation. For example, the patient may not be able to sit still, though this would not be considered akathisia, but somehow the restlessness feels like increased nervous energy.

Can you describe the disinhibition associated with mania?

Dr. Nierenberg: One of the cardinal features of mania and hypomania is a diminishment of inhibition, and therefore an increase in risk taking. But, it is important to for the clinician to gauge what is normal for the patient. For example, a patient may have lived his or her whole life "living on the edge" by doing bungee jumping, high-risk sports, or driving very fast. In other words, that is what he or she likes to do when he or she is not manic. Alternatively, disinhibition might be characterized in a patient who has always been cautious and stays within the speed limit when driving, but then suddenly starts driving 100 miles an hour without a seatbelt. That type of changed behavior reflects risk taking. Another example might be a patient suddenly making extravagant purchases or spending a lot of money without much thought. Manic or hypomanic people act more impulsively than they usually do and

take risks that can cause them or their loved ones some harm.

What can you tell us about the symptom of a decreased need for sleep?

Dr. Nierenberg: There is a marked distinction between a decreased need for sleep and insomnia. Generally, a patient with a decreased need for sleep is not upset about it at all. The clinician must determine if the patient has been sleeping less than usual and if he or she is equally rested compared to when he or she gets the normal amount of sleep. The clinician should get a sense of what the normal range of sleep for a particular patient usually is by asking questions such as the following:

- How much sleep do you need now?
- Do you have to drink a lot of coffee to stay up?
- Are you very fatigued the next day?

If the normal sleep amount is 8 to 9 hours a night, and the patient currently needs only three hours of sleep and feels fine during the day, then it is likely a true decreased need for sleep. The greater the difference between the normal amount of sleep for the specific patient when well and what they need now, the clearer the symptom is. If the difference between normal and current sleep is only a one-hour difference, it is a little fuzzy. If it is two hours, it starts to get clearer. If it is a four-hour difference, then it's unequivocally a decreased need for sleep.

Decreased need for sleep is not insomnia; rather, it is that all of the sudden this patient just does not need to sleep.

The DSM-V is proposing some additional symptoms for mania or hypomania: irritability, distractibility, psychomotor agitation. What can you tell us about these symptoms?

Dr. Nierenberg: These additional symptoms in the *DSM-V* proposal may be too nonspecific relative to these disorders.[2] Our challenge is to see which of these symptoms are more specific to the diagnoses about which we are talking. I believe that irritability is so nonspecific that it is difficult to know where it would lie as part of a diagnosis. Does it fit in the realm of bipolar disorder? Does it fit in the realm of agitated depression? Is it part of the spectrum of anxious depression? Or is it in the spectrum of MDD with anger attacks, where the patient is likely to have difficulty with anger regulation. Agitation is one of the nonspecific symptoms that can mean many things.

Persistent, pervasive, and severe irritability that is different from the usual self is among the symptoms that one could develop when manic. But, once again it cannot be taken in isolation. Irritability has to be concurrent with some of the other manic-type symptoms.

Finally, distractibility is another nonspecific symptom. People might be distracted when they are depressed, anxious, or when they suffer from any one of a multitude of cognitive problems. They can also have comorbid attention deficit hyperactivity disorder (ADHD) that has never been treated. Those with ADHD are more likely to develop MDD. Those with MDD are more likely to have ADHD as compared to the general population.

How do you treat patients who present with "mixed" depression?

Dr. Nierenberg: Treating the phenomenon of "mixed" depression is complicated.[1,3,7,8] The initial treatment plan must always rely upon and reflect the patient's history. If a patient has a clear and well-documented history of mania or hypomania, which would qualify him or her as having a diagnosis of bipolar I or II disorder, then the clinician would treat the patient for bipolar I or II in the present episode. In the absence of unequivocal, documented manic or hypomanic episodes in the past, the assumption is that the patient will more than likely present with manic or hypomanic episodes in the future, but we do not really know for sure.

How do you treat the "equivocal" group of "mixed" depressed patients who present with subthreshold mania and have no prior history?

Dr. Nierenberg: As we know from the STEP-BD program, there are a lot of patients like this. The clnicians must monitor this type of patient carefully when prescribing an antidepressent without a concomitant antimanic agent at the same time. The clinician should be on the lookout for an exacerbation of the manic symptoms that are currently present, as well as the emergence of new symptoms that might propel the patient into having a full-blown episode of hypomania or mania.

How would that influence your initial treatment plan?

Dr. Nierenberg: First, I would do a systematic interview of the patient to make sure that I detected those manic-type symptoms. The only way to do that is to use one of the various systematic diagnostic interview instruments. Otherwise, there is the risk of omission, which we all can make.

Second, I would treat the symptoms of depression itself and not necessarily add a medication that would prevent a full-blown manic or hypomanic episode. But, I would have a very heightened awareness and anticipation that this may occur. Therefore, the clinician should educate the patient on the signs and

symptoms of a manic episode as well as remain very diligent in tracking this patient's behaviors over time.

Would you ever start an antimanic agent in patients with "mixed" depression?

Dr. Nierenberg: Yes, and this decision would be based upon the previous treatment history. I would add an antimanic agent if the patient has had antidepressant-associated, manic-type symptoms emerge during treatment in the past. For example, if there was a paradoxical reaction of severe agitation in a patient following a trial of an antidepressant for depression in the past, that indicates that adding an antimanic agent would be prudent.

In the future, where do you think that the clinical presentation of "mixed" depression will fit within the diagnostic system?

Dr. Nierenberg: Right now, this type of a patient might be considered bipolar, not otherwise specified. In other words, the clinican is not exactly sure what is going on with the patient. I think as neuroscience researchers, we need to find out what the implications are not only for the depression but also for those few subthreshold manic symptoms. The *DSM-V* will at least recognize the importance of patients who have a major depressive episode with mixed manic-type features. The recognition of "mixed" depression as a distinct entity will allow us to learn more about this large group of patients and improve our treatments.

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